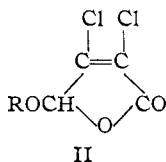
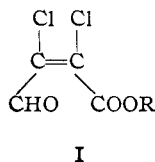


[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, MONSANTO CHEMICAL COMPANY]

Mucochloric Acid. I. Reactions of the Pseudo Acid Group

BY DAVID T. MOWRY

The chemistry of mucochloric acid was investigated fairly intensively from 1880 to 1905 principally by Hill^{1,2,3,4} and Simonis^{5,6,7} but apparently has not been studied further since. As the half aldehyde of dichloromaleic acid, it was thought to exist in two forms having normal (I, R = H) and pseudo (II, R = H) structures.



The methyl ester of mucochloric acid was thought^{3,4} to have the 3,4-dichloro-5-methoxy-2(5)-furanone structure (II, R = CH₃), because it did not react with hydroxylamine. Esters of this type are the first aliphatic pseudo esters known, a distinction erroneously claimed recently for the cyclic esters of levulinic acid.⁸ In addition to the previously reported but uncharacterized methyl and allyl esters⁶ of mucochloric acid, we have prepared the vinyl, *n*-amyl and *n*-dodecyl esters. The vinyl ester is extremely lachrymatory. These esters were found to behave like esters of a tetrabasic acid under the usual conditions for the determination of saponification numbers. This was undoubtedly caused by further degradation of the intermediate sodium mucochlorate by excess alkali, the probable end-products being sodium formate, sodium chloride and the disodium salt of α -hydroxy- β -chloroacrylic acid.⁹

Hill's assignment of the pseudo structure to the methyl ester has now been confirmed by an examination of its ultraviolet absorption spectrum (Fig. 1). It exhibits no absorption maximum in the 260–280 m μ region, indicating the absence of a chromophore containing both a carboxyl and a carbonyl group conjugated with a double bond. The spectra of 3,4-dichloro-2(5)-furanone³ (II, RO = H) and dichloromaleic acid¹⁰ have been determined for comparison.

Absorption spectral data (Fig. 1) indicate that mucochloric acid itself, in alcoholic solution, exists almost entirely in the cyclic form (II,

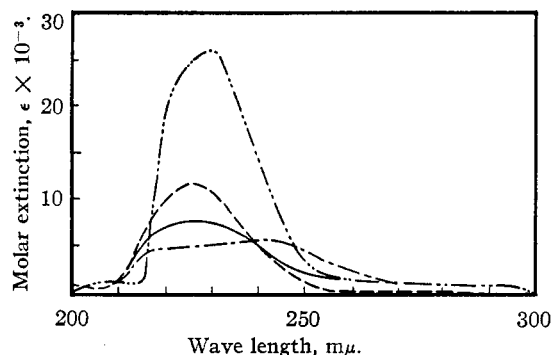


Fig. 1.—Absorption spectra of methyl mucochlorate (---), 3,4-dichloro-2(5)-furanone (— · —), mucochloric acid (—), and dichloromaleic acid (···), using 0.0008% solution in absolute ethanol with 1-cm. cell in a Beckman quartz spectrophotometer.

R = H).¹¹ This phenomenon apparently confers a degree of alcohol-like character to the acid hydroxyl group, similar to allyl or benzyl alcohols. Mucochloric acid reacted rapidly with refluxing acetic anhydride to form mucochloric acetic anhydride or 3,4-dichloro-5-acetoxy-2(5)-furanone (II, R = CH₃CO—, see Fig. 2), in 73% yield. Under similar conditions with benzoyl

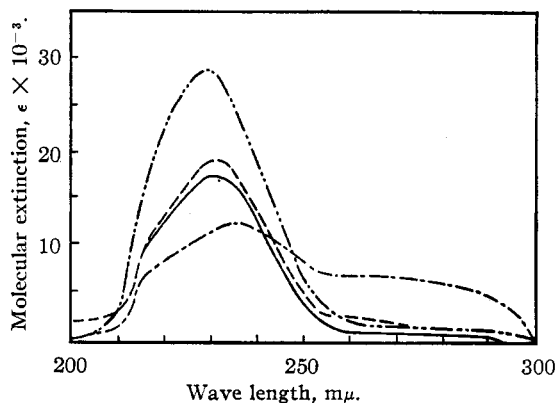


Fig. 2.—Absorption spectra of mucochloric acetic anhydride (---), mucochloric α -anhydride (— · —), mucochloric β -anhydride (—), and mucochloryl chloride (···), using 0.0008% solution in absolute ethanol with a 1-cm. cell in a Beckman quartz spectrophotometer.

chloride, it gave mucochloric benzoic anhydride in 95% yield, although this was not formed under typical Schotten-Baumann reaction conditions. Since this compound could be recrystallized unchanged from hot aqueous alcohols, it resembled an ester more than a mixed an-

- (1) Hill, *Am. Chem. J.*, **3**, 165 (1881).
- (2) Hill and Palmer, *ibid.*, **9**, 147 (1887).
- (3) Hill and Cornelson, *ibid.*, **16**, 188, 277 (1894).
- (4) Hill, Widtsoe and Dunlap, *ibid.*, **19**, 627 (1897).
- (5) Simonis, *Ber.*, **32**, 2084 (1899).
- (6) Simonis, *ibid.*, **34**, 509 (1901).
- (7) Simonis, Marben and Mermod, *ibid.*, **38**, 3981 (1905).
- (8) Langlois and Wolff, *THIS JOURNAL*, **70**, 2624 (1948).
- (9) Hill, refs. 1 and 2, has recorded analogous degradations of mucochloric acid by aqueous bases.
- (10) Ciamician and Silber, *Ber.*, **16**, 2396 (1883).

- (11) Vinogradova and Shemyakin, *J. Gen. Chem. (USSR)*, **16**, 709–720 (1946), mention similar observations on mucobromic acid.

hydride. Mucochloric acid also reacted with phenyl isocyanate in refluxing benzene solution to give mucochloric carbanilic anhydride (II, $R = C_6H_5NHCO$) in 82% yield. This was a relatively stable white solid, m. p. 116° , which showed no evidence of losing carbon dioxide below 150° . Typical open chain mixed anhydrides of carbamic acid, on the other hand, are reported to effervesce with loss of carbon dioxide at temperatures ranging from 20 to 100° .¹²

Mucochloric acid was easily dehydrated to its anhydride by refluxing in benzene or chlorobenzene in the presence of a trace of sulfuric or benzenesulfonic acid. The anhydride was isolated in two forms, an α -isomer, melting at 141 – 143° and a β -isomer melting at 180° . The ultraviolet absorption spectra, Fig. 2, showed no evidence of either isomer having an open chain structure. Hence, the isomers are presumed to be racemic and *meso* modifications of bis-(3,4-dichloro-2(5)-furanonyl) ether, which has two asymmetric carbon atoms.

Mucochloric acid reacted much more sluggishly than ordinary acids with thionyl chloride to give mucochloryl chloride⁴ in 51% yield together with 26% of the α -isomer of the anhydride. The chloride has a much milder and less lachrymatory odor than normal acid chlorides of similar volatility. As evidenced by absorption spectral data (Fig. 2), it appears to possess predominantly a 3,4,5-trichloro-2(5)-furanone structure (II, $RO = Cl$). Attempts to condense mucochloryl chloride with one mole of benzene in the presence of aluminum chloride in carbon tetrachloride, carbon disulfide or nitrobenzene solution were unsuccessful, although the use of excess benzene and aluminum chloride resulted in good yields of α,β -dichloro- γ,γ -diphenylcrotonic acid.⁵ No mucochloryl cyanide could be isolated from attempted reactions of the chloride with cuprous cyanide at temperatures ranging from 150 to 260° . No reaction was observed with magnesium in ether or dioxane.

Experimental¹³

Methyl Mucochlorate.—Mucochloric acid (Eastman Kodak Co., 423 g., 2.5 moles) was refluxed overnight with 1 l. of methanol containing 10 ml. of concentrated sulfuric acid. The reaction mixture was poured into 3 l. of water, extracted with benzene and washed with dilute solutions of sodium carbonate and hydrochloric acid. Fractional distillation through a 100-cm. Vigreux column gave 350 g. (77% yield) of methyl mucochlorate, b. p. 113° (16 mm.), n_D^{20} 1.4937. This ester was mentioned by Simonis⁸ as being lachrymatory but no physical constants or analyses are given.

Anal. Calcd. for $C_5H_4Cl_2O_3$: Cl, 38.8; mol. wt., 183. Found: Cl, 38.6; sapn. equiv., 48.0.

Allyl Mucochlorate.—Mucochloric acid (169 g., 1.0 mole), allyl alcohol (116 g., 2.0 moles), 3 ml. of sulfuric acid and 200 ml. of benzene were refluxed under a Dean and Stark trap until no more water was evolved. The

product was recovered as outlined above to give an 83% yield of allyl mucochlorate, b. p. 144 – 145° (28 mm.), n_D^{20} 1.4780.

Anal. Calcd. for $C_5H_5Cl_2O_3$: C, 45.3; H, 5.06; mol. wt., 239. Found: C, 45.3; H, 5.06; sapn. equiv., 60.1.

n-Dodecyl Mucochlorate.—This ester was prepared analogously in 84% yield. It has b. p. 192° (2 mm.), f. p. 34° , n_D^{20} (supercooled) 1.4735.

Anal. Calcd. for $C_{15}H_{26}O_3Cl_2$: C, 57.0; H, 7.77. Found: C, 57.2; H, 7.72.

Vinyl Mucochlorate.—The ester interchange method of Hermann and Haehnel¹⁴ was used. Mucochloric acid (252 g., 1.5 moles), vinyl acetate (344 g., 4.0 moles), 5 g. of mercuric acetate, 0.5 ml. of concentrated sulfuric acid and 1 g. of hydroquinone were refluxed for thirty-six hours on a water-bath. Distillation of the reaction mixture gave a crude fraction, b. p. 110 – 125° (24 mm.). This was diluted with ether, washed with dilute hydrochloric acid and water, separated and refractionated to give a 35% yield of the lachrymatory vinyl ester, b. p. 121 – 122° (20 mm.), 71 – 72° (2 mm.), n_D^{20} 1.5028. Additional vapor pressure measurements on a sample of this material have recently been reported from the University of Chicago Toxicity Laboratory.¹⁵

Anal. Calcd. for $C_5H_4Cl_2O_3$: C, 37.3; H, 2.07. Found: C, 37.4; H, 2.35.

Mucochloric Acetic Anhydride.—Mucochloric acid (42 g., 0.25 mole) and acetic anhydride (100 g., 1.0 mole) were refluxed in a 70-cm. Vigreux column, and an acetic acid fraction, b. p. 120 – 125° , was removed as it was formed. After 18 ml. had been removed in two hours the formation of acetic acid ceased. Addition of 2 ml. of benzenesulfonic acid did not cause additional generation of acetic acid. The product was then distilled to give 42 g. (73% yield) of the crude mixed anhydride, a colorless liquid, b. p. 134 – 135° (15 mm.). This was washed with water and redistilled to give 35 g. of a slightly purer material; b. p. 128° (10 mm.), n_D^{20} 1.4923. It froze to a glass when cooled with dry ice.

Anal. Calcd. for $C_6H_4O_4Cl_2$: C, 34.2; H, 1.91; Cl, 33.6. Found: C, 34.3; H, 2.33; Cl, 33.7.

An analogous material, mucobromyl acetic anhydride, m. p. 54° , was obtained by Jackson and Hill¹⁶ from mucobromic acid and acetyl chloride or acetic anhydride.

Mucochloric Benzoic Anhydride.—Mucochloric acid (33.6 g., 0.2 mole) and benzoyl chloride (28 g., 0.2 mole) were heated at 100 – 110° for three hours while hydrogen chloride was evolved. The product was poured into cold hexane, triturated and filtered to give 51 g. (95% yield) of mucochloric benzoic anhydride, m. p. 110 – 112° . The analytical sample after two recrystallizations from aqueous methanol melted at 113 – 114° .

Anal. Calcd. for $C_{11}H_6O_4Cl_2$: C, 48.4; H, 2.21. Found: C, 48.3; H, 2.15.

Mucochloric Carbanilic Anhydride.—Phenyl isocyanate (30 g., 0.25 mole), 42 g. (0.25 mole) of mucochloric acid and 100 ml. of benzene were refluxed on the water-bath for two days. The hot solution was diluted with two volumes of hexane and cooled to give 59 g. (82% yield) of slightly yellow crystals, m. p. 95 – 105° . One recrystallization from dilute ethanol gave 48 g. of white plates, m. p. 114 – 115° . An analytical sample after two more recrystallizations from ethanol melted at 116° . The principal absorption maximum in the ultraviolet region was found at $235\text{ m}\mu$.

Anal. Calcd. for $C_{11}H_7Cl_2O_4N$: C, 45.8; H, 2.45; N, 4.87. Found: C, 46.0; H, 2.73; N, 5.23.

Phenyl isothiocyanate gave no reaction under similar conditions. A reaction apparently occurred between

(12) Naegeli and Tyabji, *Helv. Chem. Acta*, **17**, 931 (1934); **18**, 142 (1935).

(13) Melting points are corrected. Ultimate analyses by the Oakwold Laboratories, Alexandria, Va.

(14) Hermann and Haehnel, U. S. Patent 2,245,131 (1941); *C. A.*, **35**, 5908 (1941).

(15) Redemann, Chaikin and Fearing, *This Journal*, **70**, 2582 (1948).

(16) Jackson and Hill, *Am. Chem. J.*, **3**, 46 (1881).

methyl isocyanate and mucochloric acid but no well-defined product could be isolated.

Mucochloric Anhydride.—Mucochloric acid (84 g., 0.5 mole), 100 ml. of benzene, 50 ml. of dioxane and 1 g. of benzenesulfonic acid were refluxed for twenty hours under a Dean and Stark trap while 9 cc. of water was removed. Ten grams of crystals were removed from the hot solution by filtration. This fraction was recrystallized twice from a mixture of benzene and dioxane (using Nuchar for decolorization) to give 5 g. of white crystals of the β -isomer of mucochloric anhydride, m. p. 180°.

The mother liquor from the hot filtration was evaporated to small volume and cooled to give 45 g. of crystals, m. p. 140–143°. Several recrystallizations from alcohol and from a mixture of benzene and hexane gave the α -isomer in slightly purer form, m. p. 141–143°.

Anal. Calcd. for $C_8H_9Cl_3O_5$: C, 30.0; H, 0.63; Cl, 44.3. Found for α -isomer: C, 30.1; H, 0.70; Cl, 44.4. Found for β -isomer: C, 30.1; H, 0.90; Cl, 43.8.

Similar products were obtained by the action of sulfuric acid or oleum on mucochloric acid in chlorobenzene solution at 0–20°. The α -isomer was also isolated as a by-product in the preparation of mucochloryl chloride below.

Mucochloryl Chloride.—Mucochloric acid (254 g., 1.5 moles) and 354 g. (330 cc., 4.5 moles) of thionyl chloride were mixed but gave very little evidence of reaction at room temperature. One gram of zinc chloride was then added and the solution was refluxed vigorously for two days after which time the evolution of hydrogen chloride and sulfur dioxide had abated. Distillation gave 145 g. (52%) of mucochloryl chloride; b. p. 109° (21 mm.), n_D^{25} 1.5252. Hill⁴ reports b. p. 101° (15 mm.) for a preparation made from mucochloric acid and phosphorus pentachloride. The absorption spectrum, Fig. 2, indicates that mucochloryl chloride is predominantly 3,4,5-trichloro-2-(5)-furanone, the principal maximum being at 235 m μ . However, a minor absorption band at 270 m μ indicates

the possibility of some α,β -dichloro- β -formylacrylyl chloride impurity.

From a higher boiling fraction, b. p. 180–185° (1 mm.), there was obtained 60 g. (26%) of mucochloric α -anhydride. This melted at 141–143° after recrystallization from a mixture of benzene and hexane.

Mucochloryl chloride was found to be relatively inert in several attempted reactions. It did not attack magnesium in refluxing ether or dioxane in the presence of traces of iodine or methylmagnesium iodide. It was largely recovered unchanged after lengthy stirring with equimolar quantities of benzene and aluminum chloride in carbon tetrachloride, carbon disulfide or nitrobenzene at temperatures up to 70°. Over 50% recovery was also observed after heating at 200° for five hours with excess cuprous cyanide. Only intractable tars resulted from longer or more drastic treatment.

Acknowledgments.—The author is indebted to Mr. D. R. Beasecker and Miss Rosella Ulm of this Laboratory for measurements of the ultraviolet absorption spectra.

Summary

The methyl, allyl, vinyl, *n*-amyl and *n*-dodecyl esters of mucochloric acid have been prepared and characterized as 3,4-dichloro-5-alkoxy-2(5)-furanones. Mucochloric acid has been dehydrated to its anhydride which has been isolated in two stereoisomeric forms. The acid has also been treated with acetic anhydride, with benzoyl chloride and with phenyl isocyanate to give the corresponding mixed anhydrides. Several observations on mucochloryl chloride have been noted.

DAYTON 7, OHIO

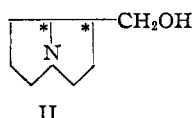
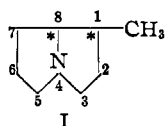
RECEIVED OCTOBER 13, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Pyrrolizidines. VI. Stereochemical Correlation of 1-Methyl- and 1-Hydroxymethylpyrrolizidine Isomers with Certain Alkaloid Products¹

BY NELSON J. LEONARD AND DONALD L. FELLEY²

With the development of a convenient method for the synthesis of 1-methylpyrrolizidine (I),³ it became possible to proceed to the separation of this product into its racemic modifications and, following this, to the resolution of the racemates. The realization of both separation and resolution now permits elucidation of the stereochemistry of the alkaloid products *l*-heliotridane and *l*-pseudoheliotridane. It has also been possible to effect the synthesis of 1-hydroxymethylpyrrolizidine (II), the structure represented in diastereoisomeric forms by the alkaloid products *l*-isoretro-necanol and *l*-trachelanthamidine.



(1) For paper V in this series, see Leonard and Shoemaker, *THIS JOURNAL*, **71**, 1762 (1949).

(2) Rohm and Haas Co., Philadelphia, Pennsylvania.

(3) Leonard and Felley, *THIS JOURNAL*, **71**, 1758 (1949).

In the synthesis of 1-methylpyrrolizidine (I) starting with nitromethane and ethyl crotonate by a three-step method involving two Michael condensations followed by reductive cyclization,³ both asymmetric centers (carbons 1 and 8) have been established prior to the reduction step, which might otherwise be stereospecific. The immediate precursor of I, diethyl β -methyl- γ -nitropimelate, results from two Michael reactions and hence should represent a mixture of two racemates. Reduction of such a mixture would be expected to yield the two diastereoisomeric racemates of I, yet in our previously described synthesis,³ only one of the racemates was obtained pure. This isomer which predominated was apparently identical with the sole 1-methylpyrrolizidine racemate obtained by the syntheses of Men'shikov⁴ and Prelog and Zalan⁵ and named by them "*dl*-heliotridane." In order to obtain both

(4) Men'shikov, *Bull. acad. sci. U. S. S. R., Classe sci. math. nat., Sér. chim.*, **5**, 1035 (1937).

(5) Prelog and Zalan, *Helv. Chim. Acta*, **27**, 531 (1944).